REMARKS

1. General Matters

1.1. The Examiner is thanked for allowing claims 4, 5, and 46, which recite a polypeptide comprising the sequence of SEQ ID NO:1 (4) or a polypeptide consisting of the sequence of SEQ ID NO:1 or 2 (46).

1.2. Claims 4, 46 and 47 have been amended to recite a "substantially pure" polypeptide so that they cannot read on mature MASP-2 as a product of nature. The basis for this amendment is at P8, L24 and P9, L18-30. SEQ ID NO:2 comprises the signal sequence of MASP-2. The mature form is believed to correspond to AAs 16-686 of SEQ ID NO:2, see P28, L2-4. The claims references to SEQ ID NO:2 have been amended accordingly. "Closed claim" coverage of SEQ ID NO:1 has been transferred from claim 46 to new claim 61.

1.3. We thank Examiners Moore and Nashat for the interview conducted telephonically on December 9. In the interview, the Examiners indicated that amendments made herewith to claims 22, 28, 46, 50-52, and 54 would put those claims in condition for allowance.

By these amendments, claim 50, which requires a minimum sequence identity of 95% to the reference sequence, is rewritten in independent form. Also, activity (i) has been amended to avoid reference to "MASP-2 activity"; the new language is based on P39, L11-14. The Examiner suggested excission of original activity (ii), serine protease activity, because amended (i) already recites C4 cleavage activity which would encompass serine protease activity. Hence activity (iii) was redesignated as (ii). Also, as requested by the Examiner, the polypeptide was required to have both C4 cleavage and MBL associating activity, not just one or the other.

1.4. We have retained a few claims (47, 49, 53) of broader scope. We would be agreeable to the cancellation of these claims by Examiner's Amendment as part of a Notice of Allowance.

1.5. New claims 57 (draft 57), 58 (draft 61), 59 (draft

63), 60 (draft 64), 61 (draft 66) are based on claims proposed in the draft amendment discussed in the interview and were deemed allowable as is (57, 58) or if made dependent on claim 50 (59, 60, 61). They were so revised

New claims 62 and 63, which parallel 61 but are dependent on 51 and 53 were suggested by the Examiner.

New claim 64 combines the limitations of 54 and 61. New claims 65 and 66 parallel 54 but are dependent on 51 and 52. New claims 67 and 68 add to 65 and 66 the limitation of 61.

1.6. New claim 69 is not dependent on 50, but rather on 47 through 53. We would be willing to cancel 69 under the terms noted in 1.4 above.

1.7. During the interview, the Examiner suggested that it might be necessary to cite SEQ ID NO:2 after each reference to "MASP-2". We disagree.

37 CFR 1.821(d) says that "where the description or claims of a patent application discuss a sequence that is set forth in the 'Sequence Listing'... reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims...."

We believe that it is possible and common to discuss a polypeptide -- its origin, its function, its tissue distribution, its regulation, etc. -- without discussing its particular sequence, and it is only the latter which can require citation of a SEQ ID NO:.

We consulted with Examiner Law, the PTO sequence listing specialist, and on December 10 he indicated that our position was correct.

Accordingly, we have amended the specification but only at pp. 15 and 44-50.

We wish to note that where "MASP-2" refers to the major form of the mature human protein, it corresponds to AAs 16-686 of SEQ ID NO:2, not to SEQ ID NO:2 per se.

1.8. Claims 70 and 71 are directed to purified human MASP-2 and are introduced in view of the inventorship issue raised in

the last section of this paper.

2. Definiteness Issues

Claims 6, 11, 22 and 28 were rejected for indefiniteness. Claims 6 and 11 have been cancelled. Claims 22 and 28 have been amended to depend from pending claim 47 rather than cancelled claim 1.

3. Utility Issue

Claims 6, 11, 22, 28, 41-45 and 47-55 have been rejected for lack of utility.

The Examiner concedes that the Thiel-Jensenius Declaration establishes "the utility of pharmaceutical compositions that comprise the mature MASP-2 protease having the amino acid sequence set forth in SEQ ID NO:2 and methods for treating patients with the composition".

Claims 6, 11 and 41-45 have been cancelled. All of the remaining claims require a polypeptide comprising a sequence which is at least 85% identical to SEQ ID NO:2 (see claim 47).

Claim 47 is supported not by a "mere allegation" of utility, but rather by the utility concededly established for the full-length sequence, and the known general correlation between fragment size and retention of activity. Moreover, because of the functional limitations of claim 47, it and its dependent claims ensure that the regions necessary for that functionality are maintained.

Given that claim 47 is admitted to read on a functional species (the full length SEQ ID NO:2 of claim 46), it is clear that a rejection for lack of utility is manifestly improper. Because of the functional limitation, claim 47 cannot read on any nonfunctional mutant/fragment. It necessarily satisfies the utility requirement of 35 USC §101. If the Examiner believes that it would require undue experimentation to identify functional mutants, then claim 47 can be rejected for lack of enablement (see below), but a §101 rejection cannot be applied

to a claim requiring an activity that confers utility, if at least one active species is disclosed. If no mutants were functional, the claim would automatically read just on the active species. See Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989), where the Board pointed out that the claims recited an activity limitation and that the assay for activity required only routine skill.

3. Description Issues

Claims 6, 11, 22, 28, 41-45 and 47-55 are rejected for lack of description. Claims 6, 11, and 41-45 have been cancelled, and claims 22 and 28 made dependent on claim 47. Hence we direct our remarks to claim 47. This claim requires that the polypeptide comprise a sequence at least 85% identical to SEQ ID NO:2.

The specification discloses SEQ ID NO:2 (see Fig. 6) and the Examiner has conceded the allowability of a claim to a polypeptide comprising SEQ ID NO:2 (claim 46).

The specification contemplates both the mature form (AAs 16-686 of SEQ ID NO:2) and the precursor polypeptide (P27, L30-P28, L5).

The specification plainly further contemplates mutants of mature MASP-2, see, e.g., P27, L21; P28, L12-14; P29, L23. It expresses a preference for mutations which qualify as conservative substitutions (P28, L25-27 and P10, L15-23).

It also expresses a preference for mutants which are "at least 85%, preferably at least 90%, and more preferably at least 95%, 98%, or 99% identical to the sequence of the reference polypeptide", P9, L31 to P10, L3, and P5, L1-4. The percentage identity is defined in such a manner than it can include appropriately sized fragments of SEQ ID NO:2, see P10, L4-13.

It is evident that applicants thought themselves entitled to coverage of mutants which were at least 85% identical to SEQ ID NO:2, consistent with claim 47.

Nonetheless, the Examiner contends that there is a lack of "effective description", i.e., what the Eli Lilly court called

"relevant identifying characteristics".

The Examiner says that "Applicant declines in Paper No. 14 to address the relevant decisional law concerning claims describing undisclosed genera... and is invited to do so in response to this communication". That "decisional law" has already been reviewed by the Examiner's superiors, and the instant action is inconsistent with the official PTO interpretation of Eli Lilly, Fiers and Amgen. Before reviewing that interpretation, we think it appropriate to point out that all three of these decisions related to claims to cDNA, not polypeptides, and not one of them related to a claim reciting a percentage identity limitation.

In Amgen and Fiers, all the applicant had disclosed was a probe and a protocol for using the probe to isolate the claimed DNA. There was not even one complete structure. Here, a complete structure is disclosed, see SEQ ID NO:2. Hence, Amgen and Fiers are distinguishable.

In Eli Lilly, the patentee had isolated the cDNA for rat insulin, but was claiming the cDNA for human insulin, mammalian insulin, and vertebrate insulin. The court declared that "a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus by showing the enablement of a representative number of species within the genus." 43 USPQ2d at 1406.

The Federal Circuit quoted with approval the CCPA's comment in In re Grimme that "it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language'". However, it refused to speculate as to what generic cDNA claims could be allowed on the basis of a single cDNA sequence.

While the Federal Circuit did not consider the vertebrate

(or mammalian) insulin cDNA genus to be adequately represented by the patentee's rat insulin cDNA, it should be noted that the Eli Lilly claim, reciting a "reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin", expects the person skilled in the art to be able to isolate the particular cDNA corresponding to a naturally occurring vertebrate mRNA, not merely to identify a mutant of rat insulin which retains activity. The '525 patent actually disclosed the amino acid sequence of human insulin, but it did not disclose the authentic corresponding cDNA.

We have reviewed the patent invalidated by Eli Lilly (4,652,525) and found it devoid of even generic teachings of mutation or mutants. Hence, Eli Lilly provides no guidance (other than the aforementioned standard) as to the proper treatment of a percentage identity claim supported by disclosure of a member species, sequence-specific comparison of that protein to homologous proteins, and general discussion of conservative substitution, mutation studies, etc.

The PTO has promulgated guidelines --which the Examiner is not at liberty to ignore-- as to the interpretation of the "written description" requirement.

Under those guidelines, for each claim drawn to a genus, the written description requirement is satisfied through "sufficient description of a representative number of species".

Disclosure of the "complete structure of a species or embodiment" satisfies the requirement for that species. Thus, the requirement is satisfied for mature MASP-2.

The question then is whether this species is "sufficiently representative". A single species can be representative of the entire genus if, given the claim limitations, there is not "substantial variation" within the genus.

The meaning of this term is elaborated upon in the Written Description Training Materials (WDTM). WDTM Example 14[1] analyzes

[1] Our last amendment cited WDTM Example 13 in support of claim 4. While claim 4 has been deemed allowable, we wish to

description for a claim to "a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B". The term "having" is interpreted as meaning "comprising". The specification is said to disclose that procedures for mutation are routine, and to provide an assay for detecting the catalytic activity of the protein".

The last paragraph of the analysis states:

> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

The PTO clearly, by its WDTM, interpretes Eli Lilly as **allowing** a single reference protein to be representative of the genus defined by a "percentage identity" claim.

The instant application discloses the complete sequence of MASP-2, the percentage identity limitation of claim 47, and assays for activity (see, e.g., Example 7; P36, L12-31; P39, L10 to P40, L11; and the references cited at pp. 1-3). Assays for serine protease activity are generally known in the art.

Claim 50 recites the same percentage identity as does WDTM Example 14 (95%) and thus is plainly within the "safe haven"

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point out that we had not cited a nonexistent Example 13 of the specification as the Examiner assumes at OA P. 6, L15.

provided thereby. Claims 47 and 49 recite somewhat broader genera (85% and 90% identical, respectively). It is respectfully urged that even when the minimum percentage identity is 85%, the considerations mentioned in WDTM Ex. 14 still apply.

A very large number of patents have issued over the years which contain generic percentage identity claims. Often, only the sequence of a single reference protein was completely disclosed. Hence, the claims in question were justified by the disclosure of that one protein coupled with more or less general teachings concerning mutation. In general, these patents did not list specific mutations, e.g., F139Y. Instead they disclosed the desired percentage identity and possibly provided other guidance, e.g., conserved sites among homologues, the general concept of conservative replacements, etc.

If there were just one such patent, the Examiner could fairly discount it as aberrational. However, when the USPTO has repeatedly allowed claims of a particular type, on the basis of such a disclosure, that constitutes evidence that our similar claims are commensurate with our similar disclosure.

The following cases illustrate the relevance of prior patents:

> Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);
>
> In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);
>
> Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);
>
> In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

There are many examples of allowed percentage identity claims from patents which disclose a single reference sequence, together with some guidance as to mutation. Only a few of these are recited in Appendix 1 below. We have deliberately confined our attention to very recent patents.

We respectfully submit that the issuance of these patents, together with the WDTM Example 14, adequately establishes that there is a consensus in the art and at the PTO that a single reference protein is normally representative of a genus defined by a minimum percentage identity limitation disclosed in the specification. We do not believe that any of them teach specific mutations (e.g., G39A) to a substantially greater extent than we do. Several of these patents use 85% (or a lower value) as the minimum percentage, and we submit that this is true of many additional patents, too. See, for example, those cited on pages H23-37 to -38 of I. Cooper, *Biotechnology and the Law* (2002).

While we have assumed above that only one species within the claim is disclosed by complete amino acid sequence, that is actually a conservative view.

At page 47 we disclose that clone ph1-3 encodes a polypeptide which differs from SEQ ID NO:2 by the mutation Asp356-Tyr. We suggest that this sequence may be an allelic variant, see P47, L15-20; although that is not certain. Nonetheless, it represents a complete alternative sequence and, if it has the recited activities, supports the claim.

Also, at P7, L20 we disclose "mature MASP-2 which has an added amino terminal methionine".

4. Enablement Issues

Claims 6, 11, 22, 28, 41-45 and 47-55 are rejected for lack of enablement. Claims 6, 11 and 41-45 have been cancelled, and claims 22 and 28 made dependent on 47. The discussion of claim 47 begins at OA page 8, line 4.

The Examiner relies upon Genentech Inc. v. The Wellcome Foundation Ltd., 31 USPQ 1161, 1168 (Fed. Cir. 1994). The Examiner interprets this decision as holding that the recitation of the native amino acid sequence, coupled with general teachings concerning mutation, could not enable even a claim like 52, which allows for mutation of just 6 AAs (1%). That is erroneous.

The Genentech decision related solely to the issue of infringement. The issue of enablement was not presented to the Court for decision. Hence, any comment that the court made which related to enablement would be considered dictum. Dictum is not binding.

The issue in Genentech required construction of the claim term "human plasminogen activator", in order to determine whether a "variant", FE1X, infringed. The court said that there were four possible definitions of this term, ranging from a recombinant protein with the same sequence as native tPA to a protein "is capable catalyzing the conversion of plasminogen to plasm, binds to fibrin, and is classified as a t-PA based on immunological properties". Id. 1167.

The part of the opinion on which the Examiner relies is that in which the court says "the determination of which permutations are operative would thus require an undue amount of experimentation". Id., 1168 Why the "thus"? Because Genetics Institute had expended $20 million dollars and 130 man years to develop FE1X and Genentech had filed patent applications directed to the variant FE1X (the variant accused of infringement), thus implying that this variant was nonobvious over native tPA.

We believe that the Court's consideration of permutations other than the very substantial (less than 85% identical) one represented by FE1X (which lacked the finger region, most of the E region, and a carbohydrate chain of the K1 region, had only 40% wild-type fibrin binding, and had a 10 fold greater half-life) was perfunctory.

The Examiner also ignores the point that even though the specification made reference to preparation of "derivatives" (mutants), Burroughs Welcome chose to claim only "human plasminogen activator". It did not recite a "polypeptide with activity X which is specifically bound by an anti-tPA antibody", as would have been consistent with the court's "fourth definition". It does not specifically and explicitly claim mutants by a percentage identity limitation. The court aptly referred to "the limited form in which the claims are drafted".

Even if the court had squarely ruled on enablement, it would have been in the context of the art as it existed in 1980, when the Burroughs Welcome priority application was filed. The instant provisional application was filed in 1997.

There have been some extremely important developments in the interim. These include the techniques of:

(1) alanine-scanning mutagenesis
(2) homologue-scanning mutagenesis
(3) combinatorial library design and screening.

These techniques facilitate the identification of which positions of tolerant of mutation (conserved positions) and which replacements are accepted.

In alanine scanning mutagenesis, which was first practiced by Cunningham, et al., Science, 244:1081-85 91989), a set of single alanine substitution mutants is prepared and screened. In each mutant, a single non-Ala residue is changed to alanine, but the set collectively explores the effect of mutation either throughout the entire protein, or in a particular region of interest. Alanine is used because (1) it is the most common

amino acid residue in proteins, (2) it has a small side chain, and therefore is not likely to sterically hinder other residues, and (3) its side chain ($-CH_3$) does not form H-bonds, but is not especially hydrophobic.

Cunningham scanned residues 54-74 of hGH. For other uses of Ala-scan mutagenesis, see Yu, et al., J. Mol. Biol., 249:388-97 (1995) (complete scan of a single disulfide derivative of the 58-residue protein BPTI); Allen, et al., Nature, 327:713 (1987) (Ala-scan of residues 52-61 of hen egg white lysozyme); Ruf, et al., Biochemistry, 33:1565-72 (1994) (Ala-scan of residues other than Gly, Pro and Cys; multiple Ala mutants examined first, then single Ala mutants); Williams, et al., J. Biol. Chem., 270:3012-6 (1995) (Ala-scan in insulin receptor of (1) charged amino acids, (2) aromatic residues, and (3) residues adjacent to (1) or (2), other than prolines, cysteines, or potential N-linked glycosylation sites); Kelly and O'Connell, Biochemistry, 32:6828-35 (Ala-scan of antibody CDR).

In homologue scanning mutagenesis, which was first practiced by Cunningham, et al., Science, 243:1330-36 (1989), a set of hybrids of two homologous proteins is compared. In each mutant, a segment of one protein is replaced by the corresponding segment of a homologous protein. The affected segment location varies from one member of the set to another.

In a combinatorial library, mutant proteins are displayed on the surface of phage. These proteins differ at predetermined residue positions as a result of the randomization of the corresponding codons in the DNAs which encode them.

The mutations can be focused (e.g., six positions each varied through 20 different amino acids) or diffuse (e.g., 26 positions each of which can be either the wild type AA or a replacement). See Ladner, USP 5,223,409 (based on a 1989 application). The techniques of alanine-scanning mutagenesis and combinatorial mutagenesis have been combined, see Gregoret and Sauer, Proc. Nat. Acad. Sci. (USA), 90:4246-50 (1993). If it is feasible to screen a library of 10^{10} mutants, then the combined

effects of up to 30 different Ala substitutions (2^{27}~10^{10}) can be studied in one experiment.

In the Genentech case, the court said that "there is no basis provided in the specification for determining which of these permutations are operative and which are not". Id., 1168 Here the specification provides guidance as to methods of identifying conserved positions. Thus, at page 29, lines 8-15, it teaches:

> To design functionally equivalent polypeptides, it is useful to distinguish between conserved positions and variable positions. This can be done be aligning the sequence of MASP-2 cDNAs that were obtained from various organisms. Skilled artisans will recognize that conserved amino acid residues are more likely to be necessary for preservation of function. Thus, it is preferable that conserved residues are not altered.

While it does not refer specifically to combinatorial libraries, it teaches at P28, L30 to P29, L1 that

> Polypeptides that are functionally equivalent to MASP-2 (SEQ ID NO:2) can be made using random mutagenesis techniques well known to those skilled in the art (and the resulting mutant MASP-2 proteins can be tested for activity).

With regard to the choice of amino acid replacements, it teaches that conservative substitutions are preferred, see P10, L15-23:

> In the case of polypeptide sequences which are less than 100% identical to a reference sequence, the non-identical positions are preferably, but not necessarily, conservative substitutions for the reference sequence. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine, and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine.

The Federal Circuit did not address the import of such teachings when it construed the Burroughs Wellcome claim.

The Examiner concedes that the enablement standard does not require that one make and screen any and all possible alterations. (OA P9, L13-16). However, the Examiner appears to believe that claims to mutants are permissible only if the locations of the mutations are specifically identified in the specification and claims (OA P8, L7-12 and 22-P9, L5).

Applicants' Figure 2 presents an alignment of MASP-2 with MASP-1, Clr and Cls. These proteins all activate the MB lectin pathway (P1, L26-L32; P48, L14-16).

The overall sequence of identity of MASP-2 with the other three proteins is only 39-42%, and the overall sequence similarily is 39-52%. Since the proteins have similar activity, they clearly are highly tolerant of mutation. The recitation of a minimum percentage identity of 85% was conservative.

According to the specification, MASP-2 has the same domain organization as the other three proteins: a first Clr/Cls-like domain, an EGF-like domain, a second Clr/Cls-like domain, a first CCP domain, a second CCP domain, and a serine protease domain. MASP-2 is expected to be activated by cleavage between the Arg at the end of the second CCP domain and ILE at the beginning of the serine protease domain, generating a heavy chain and a light chain held together by a disulfide bond. The relevant Arg-Ile are at positions 444-445 of MASP-2. (P48, L25-27).

The specification also notes (P49, L6-8) the triad of residues constituting the active center of the protease domain, namely His-468, Asp-517 and Ser-618.

The alignment of Fig. 2 also identifies residues which are identical in all four species (P48, L31-32).

P29, L8-15 plainly teaches that it is preferable that conserved positions not be altered. Skilled workers would also recognize that residue positions can differ in the degree of conservation. At one extreme, the same residue appears at the indicated position in all homologues. At the other extreme, a

different residue is exhibited by every homologue at that position. A skilled worker, seeking to mutate a protein while retaining its activity, would favor mutation at the positions of highest variability. There are 135 positions which are different in all four proteins of Fig. 2.

Moreover, based on page P10, L15-23, the skilled worker could seek positions with maximum dissimilarity (i.e., taking conservative substitution into account), not merely maximum variability in identity. Thus, for safety's sake, one choosing a position to mutate could pick one which is dissimilar in all four proteins of Fig. 2. For example, in the EGF domain, AA 130 is Pro in MASP-2, Glu in MASP-1, Ser in Clr and Phe in Cls. None of these exchanges qualify as conservative substitutions.

5. Inventorship Issue

This issue is being raised by Applicants, in compliance with the duty of disclosure.

The instant application is a division of 09/054,218, filed April 2, 1998, which claims the benefit of 60/042,678, filed April 2, 1997.

The presently named inventors are Jensenius and Thiel. The Examiner should consider whether any other individuals should be named as inventors. The Examiner's attention is respectfully directed to Ref. V from the PTO-892 attached to the January 28, 2003 office action. This named Thiel, Vorup-Jensen, Stover, Schwaeble, Laursen, Poulsen, Willis, Eggleton, Hansen, Holmskov, Reid and Jensenius as co-authors. The citation is Nature, 386:506 (April 1997).

There is a counterpart application, 09/874,238, filed June 4, 2001, which is also a division of 09/054,218. In the '238 prosecution, on May 27, 2003, antibody claims were rejected under 35 USC 102(a) as being anticipated by that reference, which was published on April 2, 1997. (In that case, the Examiner took the position that the antibody claims were not supported by the provisional application.)

In the course of preparing the response (filed October 27, 2003) to that office action, it came to Counsel's attention that one of the authors of that publication, Cordula Stover, had refused to sign a "disclaiming declaration".

Prior to Stover's involvement, the MASP-2 protein was isolated and partially sequenced, and a 300 bp cDNA was generated, on the basis of the AA sequence information, and used as a probe. A 1.8 kb clone was isolated which included the DNA encoding part of the serine protease domain of MASP-2.

Cordula Stover's supervisor, William Schwaeble, heard of the project and offered to help with isolating and sequencing further clones. As explained in the disclaiming declaration (copy enclosed) executed by Schwaeble:

> Working as a graduate student under guidance of Wilhelm Schwaeble, Cordula Stover cloned and sequenced cDNA sequences encoding i.a. full-length MASP-2. This was accomplished with the aid of a 300 bp cDNA fragment cloned by the TVJ. Three different cDNA clones were sequenced. One (A) represents the full length was found to encode a protein of 622 amino acids showing about 40% sequence identity to C1r, C1s and MASP-1. Another clone (C) represented the N-terminal part of clone A with additional four amino acids not found in A. The size of C (ORF of 540 bp) agrees with it representing mRNA encoding the truncated form of MASP-2. The third clone (B) has a 5' end almost identical to C but in addition an ORF of 558 bp with no similarity to A.

Stover has not disputed this description of her role. However, sometime between October 3 and October 7, 2003, she refused to sign a parallel disclaiming declaration. (See pertinent extract from emails.)

The instant claims are directed to polypeptides. The MASP-2 polypeptide was isolated and partially sequenced prior to Stover's first involvement in the project. Nor did she suggest mutating the polypeptide. The hybridization and sequencing work she carried out were of a routine character; mere technician's

work. It is respectfully urged that under these circumstances Stover cannot be considered to have made an inventive contribution to the instant polypeptide claims.

Applicants, who immunopurified and partially sequenced MASP-2, believe that they conceived MASP-2 in a sufficiently specific form to be considered the only inventors, the later work of Schwaeble, Stover, etc. simply inuring to their benefit.

Prior to the involvement of Schwaeble and Stover, MASP-2 was defined as follows:

1) it is a protein occurring in human plasma (P43, L1);

2) it has affinity for mannan- and N-acetyl glucosamine-derivatized sepharose beads, in a calcium dependent manner (P43; L1-14);

3) it has an apparent molecular weight of 76 kDa when analyzed by SDS-PAGE under non-reducing conditions (Fig. 1; P47, L26-27), and of 52 kDa when analyzed by SDS-PAGE under reducing conditions (P43, L15-18) (see also P44, L2-5);

4) it cross-reacts with chicken antibody raised against a bovine lectin preparation (P43, L15-19);

5) it comprises the four partial amino acid sequences which are underlined in Fig. 6 (P43, L19-20; P43, L31-P44, L1); the four underlined sequences correspond to AAs 16-56, 108-134, 377-388 and 410-417 of SEQ ID NO:2;

6) the aforementioned partial sequences showed similarity to MASP-1, whose sequence was known in full (P43, L20-22; the similarity of the full-length proteins is 52%, see P49, L18);

7) when digested with trypsin, it yields the fragments referred to at P46, L4-8, the major peaks of which correspond to three of the four partial sequences noted in point 4 above.

We do not believe it reasonable to think that there is an alternative polypeptide which satisfies all of these criteria. Consequently, we believe that neither Schwaeble nor Stover need be considered inventors of MASP-2 as claimed.

Disclaiming declarations were executed, not only by Schwaeble, but also by Vorup-Jensen, Laursen, Poulsen, Willis,

Eggleton, Hansen, Holmskov and Reid. (See the file of 09/874,238). These declarations are identical to the one executed by Schwaeble and enclosed herewith.

For the sake of completeness, the Examiner should consider whether any of these other individuals should be named as inventors. In this regard, we note that the N-terminal and tryptic peptide sequencing was carried out by Willis at the request of Thiel and/or Jensenius. We do not know at this time the extent of their supervision of or control over Willis' work.

The disclaiming declarations are formally deficient in that (1) they do not contain the usual penalty clause and (2) it is unclear whether the concession of the right of commercial exploitation and patenting" relates to inventorship or to ownership. Hence, we would prefer to replace them with a Katz-type declaration executed by Thiel and/or Jensenius, but containing essentially the same recitation of facts.

We await the Examiner's guidance on the inventorship issue before drafting the proposed declaration, so we can make sure it addresses all relevant factual questions.

Respectfully submitted,

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Enclosures
-Schwaeble disclaiming declaration
-extracts from emails
-Appendix 1

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Discovery of MASP-2

The protein now designated MASP-2 was isolated and identified in Aarhus by Steffen Thiel and Jens Chr. Jensenius through its reaction with a chicken antibody.

The N-terminal amino acids of the protein was sequenced in Oxford by Anthony C. Willis from blots on PVDF provided by the Aarhus group. Antibody against a synthetic peptide representing the N-terminal 20 amino acids reacted with the protein as well as with a polypeptide of 20 kDa. The 20 kDa peptide was N-terminally sequenced by ACW and found to be identical to the N-terminal sequence of the 50 kDa protein. Further, ACW sequenced some internal peptides of the protein and the 20 kDa form. These sequences established the protein as being related to MASP-1, C1r and C1s. The sequences also established the 20 kDa peptide as being a truncated form of the 50 kDa protein.

The Aarhus group showed the protein as well as the truncated form to be associated with mannan-binding lectin. Uffe Holmskov, Odense, was involved in this finding through ongoing discussions.

In Aarhus graduate student Thomas Vorup Jensen generated by RT-PCR a 300 bp cDNA fragment from liver RNA using oligonucleotides deduced from the peptide sequences. The amino acid sequence deduced from the 300 bp oligonucleotide encompassed the peptides used for constructing the oligonucleotides as well as another of the sequenced peptides. The derived sequence further emphasized the similarity of the new protein to MASP (MASP-1) and also the relationship to C1r and C1s.

TVJ working in Kenneth B. M. Reid's laboratory in Oxford with guidance of KBMR and Paul Eggleton used the 300 bp as probe for cloning cDNA from liver libraries and isolated a 1.8 kb clone. The sequence revealed the presence of the serine protease domain, although the C-terminal part of this was missing. Also missing (compared to the later obtained full length clone) was the 2nd C1r/s domain.

Wilhelm Schwaeble heard of the project and offered his help with isolating and sequencing further clones. The aim of this was to establish the full sequence of the mRNA and thereby also the deduced amino acid sequence. This work would also allow for the synthesis by recombinant technique of the recombinant protein. The synthesis of the recombinant protein as well as of MASP-1 and possibly also MBL was allocated to TVJ to be part of his PhD project aimed at studying the structure and function of the MBL/MASP complex. This work was designed to be carried out in collaboration with KBMR and Robert B. Sim in Oxford as well as at the Aarhus laboratory.

With the use of the 300 bp RT-PCR generated probe, the cloning and sequencing was successfully carried out in WS's laboratory in Leicester, largely by graduate student Cordula Stover. Three different cDNA clones were sequenced. One (A) represents the full length was found to encode a protein of 622 amino acids showing about 40% sequence identity to C1r, C1s and MASP-1. Another clone (C) represented the N-terminal part of clone A with additional four amino acids not found in A. The size of C (ORF of 540 bp) agrees with it representing mRNA encoding the truncated form of MASP-2. The third clone (B) has a 5' end almost identical to C but in addition an ORF of 558 bp with no similarity to A.

To the best of my knowledge the above is a true account of the identification of MASP-2. Being coauthor of the first publication on MASP-2 I furth r hereby state that I concede that the rights of commercial exploitation and patenting resulting from the first publication (Nature April 1997) belong to Steff n Thiel and Jens Chr. Jensenius

Date: 2/4/97

Signature: M. Jensenius

Wilhelm Schwaeble

USSN - 09/874,198

Appendix 1

- Draetta 5,981,699

Filed: May 23, 1994
Primary Examiner: Achutamurthy, Ponnathapura

1. A substantially pure preparation of an hUCE polypeptide comprising an amino acid sequence at least **95%** homologous to SEQ ID NO. 2, which polypeptide catalyzes ubiquitin conjugation.

4. A recombinant hUCE polypeptide comprising an amino acid sequence at least **95%** homologous to SEQ ID NO. 2, which polypeptide specifically binds at least one of an E6-AP protein, a papillomavirus E6 protein, or p53.

- Sheppard, 6,265,544

Filed: July 17, 1998
Primary Examiner: Achutamurthy; Ponnathapu
Assistant Examiner: Tung; Peter P.

1. An isolated polynucleotide encoding a polypeptide comprising a sequence of amino acid residues that is at least **75%** identical in amino acid sequence to residues 26-281 of SEQ ID NO:2, wherein said sequence comprises:

Gly-Xaa-Xaa or Gly-Xaa-Pro repeats forming a collagen domain, wherein Xaa is any amino acid; and

a carboxy-terminal globular portion; wherein a characteristic of said polypeptide is stimulation of TF-1 cell adhesion.

9. An isolated polynucleotide according to claim 1, wherein any differences between said polypeptide and residues 26-281 of SEQ ID NO:2 are due to conservative amino acid substitutions.

- Williams, 6,642,022

Filed: June 5, 1995
Primary Examiner: Spector; Lorraine
Assistant Examiner: Lazar-Wesley; Eliane

1. A purified and isolated recombinant nucleic acid encoding a type A human platelet-derived growth factor receptor polypeptide (A-hPDGF-R), or fragment thereof, wherein said fragment comprises at least about 13 amino acid residues, wherein the polypeptide has greater than 80% percent amino acid sequence identity to SEQ ID NO:4, and wherein the polypeptide has PDGF receptor activity.

- Hayden 6,617,122

Primary Examiner: Prouty; Rebecca E.
Assistant Examiner: Steadman; David J.

33. A process for identifying a compound that modulates lipid transport across a mammalian cell that includes a cell membrane that includes ABC1 polypeptide comprising an amino acid sequence with least **85%** identity to the amino acid sequence of SEQ ID NO: 1 and having lipid transporting activity, comprising testing said mammalian cell wherein said cell includes a lipid selected from the group consisting of phospholipid and cholesterol, under conditions promoting transport of said lipid across said membrane, and comparing transport of said lipid in the presence and absence of a test compound whereby a difference in said transport indicates modulation, thereby identifying said compound as a modulator of lipid transport.

- Sheppard, 6,498,235

Primary Examiner: Eyler; Yvonne
Assistant Examiner: Harris; Alana M.

7. An isolated polypeptide comprising a sequence of amino acid residues that is at least **80%** identical to a amino acid residue

21 to amino acid residue 142 of SEQ ID NO:2, wherein said polypeptide specifically binds with an antibody that specifically binds with a polypeptide having the amino acid sequence of SEQ ID NO:2.

8. An isolated polypeptide according to claim 7, wherein any difference between said amino acid sequence of said isolated polypeptide and said corresponding amino acid sequence of SEQ ID NO:2 is due to a conservative amino acid substitution.

9. An isolated polypeptide of claim 7, wherein the amino acid percent identity is determined using a FASTA program with ktup=1, gap opening penalty=10, gap extension penalty=1, and substitution matrix=blosum62, with other parameters set as default.

- Wisniewski 6,497,880

Primary Examiner: Siew; Jeffrey

2. An isolated polypeptide comprising an amino acid sequence that is at least **95%** homologous to the protein encoded by SEQ ID NO:5, wherein the polypeptide comprises a peptide of at least 8 contiguous amino acids of the protein encoded by SEQ ID NO:5, wherein the peptide binds to a major histocompatibility complex molecule, and wherein percent homology is determined according to an algorithm incorporated in a protein database search program used in BLAST (BLAST.TM., a computer program) or DNA STAR MEGALIGN (DNA STAR MEGALIGN.TM., a computer program).

- Bertin, 6,482,933

Primary Examiner: McGarry; Sean

1. An isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence that is at least **85%** identical to the sequence of SEQ ID

NO:55, wherein the percent identity is determined using the ALIGN program in the GCG software package, using a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4.

- Sidransky 6,476,206

1. A cDNA molecule which encodes a p40 protein having an amino acid sequence which is at least **99%** identical to SEQ ID NO:2, wherein percent identity is determined using a Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

[No disclosure of broader variation than 1%]

- Holtzman 6,410,232

Primary Examiner: Campbell; Eggerton A.

1. An isolated polypeptide comprising an amino acid sequence which is at least **55%** identical to the amino acid sequence of SEQ ID NO:2 with or without the signal peptide or an amino acid sequence encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98546.

2. The isolated polypeptide of claim 1, which comprises an amino acid sequence which is at least **75%** identical to the amino acid sequence of SEQ ID NO:2 with or without the signal peptide or an amino acid sequence encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98546.

3. The isolated polypeptide of claim 2, which comprises an amino

acid sequence which is at least **85%** identical to the amino acid sequence of SEQ ID NO:2 with or without the signal peptide or an amino acid sequence encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98546.

4. The isolated polypeptide of claim 3, which comprises an amino acid sequence which is at least **95%** identical to the amino acid sequence of SEQ ID NO:2 with or without the signal peptide or an amino acid sequence encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98546.

5. The isolated polypeptide of claim 1, 2, 3, or 4 wherein the percent identity is calculated using the Wisconsin GCG sequence alignment program GAP.

6. The isolated polypeptide of claim 1, 2, 3, or 4 wherein the polypeptide comprises an amino acid sequence which is at least **85%** identical to a follistatin cysteine-rich domain selected from the group consisting of the follistatin cysteine-rich domain comprising amino acid residues 97 to 167 of SEQ ID NO:2 and the follistatin cysteine-rich domain comprising amino acid residues 171 to 243 of SEQ ID NO:2.

7. The isolated polypeptide of claim 6, wherein the follistatin cysteine-rich domain comprises amino acid residues 97 to 167 of SEQ ID NO:2.

8. The isolated polypeptide of claim 6, wherein the follistatin cysteine-rich domain comprises amino acid residues 171 to 243 of SEQ ID NO:2.

9. The isolated polypeptide of claim 1, 2, 3, or 4, wherein the polypeptide comprises an amino acid sequence which is at least

85% identical to the follistatin cysteine-rich domain comprising amino acid residues 97 to 167 of SEQ ID NO:2 and the follistatin cysteine-rich domain comprising amino acid residues 171 to 243 of SEQ ID NO:2.

- Crabtree 6,388,052

Primary Examiner: Schwartzman; Robert A.
Assistant Examiner: Wang; Andrew

1. An isolated polypeptide comprising an amino acid sequence which is at least **90%** identical to at least 20 consecutive amino acids of SEQ ID NO: 38, wherein the percent identity is determined with the algorithm GAP, BESTFIT, or FASTA in the Wisconsin Genetics Software Package Release 7.0, using default gap weights.

Kim Palle Jens n

Fr m: Jens Christian Jensenius [j.c.jensenius@immunology.au.dk]
Sent: 7. oktober 2003 10:20
To: Cordula Stover
Subject: Re: signature

Dear Cordula,

Thank you for your mail. I certainly think that you deserve, and wish for you, a successful career. While I shall not lay claim to being an expert on these matters, I have been involved on a number of occasions, and my experience is that IPR is rather different from allocating scientific credit, where emphasis, contrary to IPR, is to a large extend based on the invested hard work. It is entirely a different world.

The best thing for me now is probably to leave the matter at our end to the patent agency.

Best wishes,

Jens

> Dear Jens.
> Yes, I have problems signing the paper on MASP-2 discovery thereby conceding that the rights of commercial exploitation and patenting resulting from the first publication (Nature April 1997) belong solely to you and Steffen.
> I am on a successful career and have the obligation to myself to make use of any source I have co-explored.
> With kindest regards
> Cordula
>
> on 3/10/03 16:51, Jens Christian Jensenius at j.c.jensenius@immunology.au.dk wrote:
>
> > Dear Cordula,
> >
> > Sorry to bother you again. Please, tell me if you have problems signing the paper on MASP-2 discovery.
> >
> > If, for some reason you decide not to sign, I shall have to sign a statement on your situation - being a PhD student with Wilhelm - etc etc - and this will be legally valid - can obviously be challenged - BUT the agency and the lawers seem to prefere all documents being the same. Your signature is the only one missing.
> >
> > Thus it will be convenient if you could, please, sign and return it to the the agency ASAP.
> >
> > Best wishes, Jens

<<<<<<<<<<<<<<<<<<

(copy of mail 19/9 03)

Dear friends and collaborators,

I have been rquessted to solicit your signatures on the attached document concerning patenting MASP-2.

The patent office originally asked for signatures only from those not at the time being students under supervision, so I got signatures from everybody except from the four of you.

Now, of course, I am out a bit late and thus ask you kindly to sign - do not forget the date (and, please, name also in block capitals) - and fax it to:

Kim P. Jensen
(assistent for Susanne Høiberg)
HØIBERG A/S
St. Kongensgade 59 A
DK-1264 Copenhagen K
Telephone: +45 3332 0337
Telefax: +45 3332 0384

and also to forward the original to him.

Thanks and best wishes,

Jens
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